cases the individual may reach middle life without suffering any ill-effects. The same is true of small defects in the lower portion of the muscular septum as in Case II. Where the defects are large, and particularly if other anomalies are present, cyanosis and dyspnea are the rule. Attacks of syncope following any exertion as described in Case I are not uncommon. These patients are prone to develop infections, particularly endocarditis and pulmonary tuberculosis.

The physical signs resulting from defects in the septum are described in detail by Abbott.[3] They are most intense over the central portion of the precordium, over the third and fourth ribs, just to the left of the sternum, because the septum is situated here. In brief there is usually hypertrophy of the right ventricle, and in the case of large defects precordial bulging and visible pulsation. A thrill can be felt directly over the septum, sometimes over the entire precordium. Murmurs, systolic as a rule, can also be heard best in this region and are not transmitted to the vessels of the neck. The intensity of the murmur is not always commensurate with the size of the defect.

On account of the interchange of blood between the two ventricles there is usually cyanosis. Hippocratic finger-tips and polycythemia are common accompaniments of the condition.

The two cases reported here are typical examples of congenital interventricular septum defects. Case I is an instance of multiple defect, being accompanied by pulmonary stenosis. This is a common combination and is attributed, according to the more recent theory of Keith, to an incomplete development of the infundibulum cordis. The defect in Case II is believed, in the absence of all signs of inflammatory reaction, to be congenital and due to incomplete development. By reason of its location it must be classed among the rare anomalies of the septum. The causes of developmental defects in this location are not understood.

THE TREATMENT OF HYPERTOXIC CASES OF TYPHOID FEVER BY TRANSFUSION WITH RECENTLY ARTIFICIALLY IMMUNIZED BLOOD.*

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It is with a certain degree of temerity that I approach another discussion of so hackneyed a subject as typhoid fever. Since the introduction of the name "Fièvre Typhoide," by Louis,[1] in 1839, medical literature has been flooded with publications on this subject. A review of this literature is at once inspiring and instructive. No better example of scientific medical progress can be found in all history. Rational therapy depends upon an accurate differential diagnosis, and, in this instance, there is a striking example of the evolution of modern diagnostic methods; that is, the correlation of bedside observation and clinical experience and the more accurate laboratory methods.

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[3] Loc. cit.

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It is not within the scope of this paper to review in detail the history of typhoid fever, with the exception of the progressive steps in the methods of treatment, especially specific therapy. However, one cannot pass without recalling a few of the salient facts in history to which are attached the names of the pioneers in this field.

Although this discussion is particularly in the interest of the treatment of typhoid fever along specific lines, and not those of a symptomatic nature, a few outstanding facts in the development of our ideas of the treatment of this disease cannot be ignored. No consideration of treatment would be complete without mentioning methods of prevention. This can be briefly discussed under three heads: (1) It might be possible to immunize all individuals; however, this immunity is not permanent and is only relative and might be overcome by a massive infection. (2) The destruction of all the organisms in the excreta, but this method offers the difficulty of discovering all carriers and the mild undiagnosed cases. (3) The protection of all foods and water. by proper hygienic measures. Since none of these methods is flawless they are all of equal importance.

The rather unimportant role of drug therapy hardly merits discussion here. The introduction of a high caloric diet marks one of the great steps in advance in the treatment of typhoid fever. It has been shown by Coleman and Du Bois[2] that a diet rich in carbohydrates maintains a nitrogen equilibrium best and prevents the great emaciation so often seen, and perhaps the cause of death in many cases. This conception of the dietary management of typhoid patients may be regarded as of equal importance with any other step forward in the conquest of this disease.

The judicious use of hydrotherapy is an important one, water being used both internally and externally. Of historic interest only is the Brand method of putting the patient in a tub bath at 65° F. Although heralded by Brand[3] as the ideal method of rapidly reducing the hyperpyrexia, it was found to be fraught with many dangers and has been generally discarded.

The use of typhoid vaccine as a therapeutic agent has been the source of many clinical experiments and reports. Fraenkel[4] was the first to use the vaccine by the subcutaneous method, followed by Collison,[5] Krumbhaar and Richardson,[6] Zupink, Müller and Leiner,[7] and many others. They all report a reduction in the mortality and the length of the disease. Working independently, Ichikawa[8] and Kraus and Mazza[9] introduced the intravenous method with very striking results. Many cases showed a fall of temperature by crisis, and the duration and severity of the disease were materially reduced in many others. It was soon discovered, however, that the same results could often be obtained with any foreign protein, as other bacteria, proteose, albumose, etc. It has also been observed that this method is not unattended with danger.

Labbe and Moussand,[10] following the original work of Letulle and Mage,[11] used colloidal gold solution by the intravenous route in the treatment of moderately severe and grave cases. They report a reduction in the general symptoms of infection and intoxication, shortening of the disease and a reduced mortality.

The use of a specific immune serum would seem the logical treatment of typhoid fever from the theoretic standpoint, and this has been the goal of many investigators. Numerous immune sera obtained from animals, especially horses and goats, have been used. Most of them have been reported with great enthusiasm by the originator, but only with fairly encouraging results by the subsequent observers. Chantemesse[12] prepared a serum by injecting horses with a soluble typhoid toxin. His therapeutic dose is a very small quantity injected subcutaneously, and only one dose is used. His results in 1000 cases were very encouraging, the mortality being reduced to 4.3 per cent, a very low average for Paris at that time. Besredka[13] produced a serum by injecting horses with the endotoxins obtained from dried cultures of typhoid bacilli. The observations of Besredka and the other workers along this line have not been of any practical value. Ludke[14] prepared an antiendotoxic serum from goats, and reports encouraging results. Garbat and Meyer[15] report favorable experimental results with serum obtained by injecting animals with sensitized typhoid bacilli, and other animals with untreated organisms, pooling the sera of the two. Rodet[16] and his co-workers report the most favorable results in the treatment of typhoid fever with specific serum. He immunizes horses with living bouillon cultures and endotoxins. The immune serum is given in repeated subcutaneous doses, the quantity varying from 10 to 20 cc. He reports a marked shortening of the disease and a rapid reduction of the height of the temperature. His results have been confirmed by Odilhan,[17] and Remond and Minvielle[18] and others. Stokes and Fulton[19] report a serum obtained by injecting hogs with increasing doses of bouillon cultures, producing a serum with an agglutination titer of $\frac{1}{450000}$. Its use in 23 cases showed favorable results.

Von Jaksch[20] (1895) was apparently the first to make use of the immune serum of convalescents and the results obtained were very favorable. His work was confirmed a few years later by Walger[21] (1898). This fertile field of investigation, the use of immune human serum, remained untouched for almost ten years. Petrovitch[22] (1915) employed the serum of convalescent or immunized individuals in the treatment of 500 cases with a mortality of 4.3 per cent. In 1000 control cases treated without serum the mortality was 12.8 per cent. He usually used about 10 cc intravenously. This was done in the Serbian army.

Koenigsfeld[23] reports some very interesting experiments in the treatment of typhoid fever with the patient's own serum. He gives daily intravenous injections of serum in doses of 2.5 to 4 cc. In 26 cases treated there was a marked improvement characterized by a reduction of temperature, shortening of the disease, improvement in the sensorium, and especially good results in the comatose cases. These finding were confirmed by Meyer.[24]

The use of immune blood or blood serum from convalescents in the treatment of infectious diseases is by no means a new procedure. It has been attempted in a great variety of conditions. Scarlet fever has been treated by injections of blood serum and whole blood from convalescents, both subcutaneously and intravenously, with especially good results in the very toxic cases, as reported by Weaver.[25] The recent epidemics of influenza found many adherents of serotherapy, convalescent serum and whole blood being used intravenously. Favorable reports were made by Stoll,[26] and O'Malley and Hartman,[27] but the general consensus of opinion was not so encouraging. When it is remembered that the pneumonia complicating the influenza was the result of a secondary invader and that this secondary infection varied with the individual and the locality, the serum or blood in this instance cannot be properly classed as specific. Very recently convalescent serum has been used as a prophylactic and therapeutic agent in measles, and the results reported from Germany are exceedingly encouraging. Many other examples of attempted specific therapy using convalescent serum could be enumerated. However in none of them has it been possible to demonstrate any appreciable amounts of protective antibodies.

Typhoid fever presents an entirely different problem. By means of the well-known Widal reaction it is possible to demonstrate the agglutination titer of the serum. While there are probably many different protective antibodies in the circulating blood, this is our only index. The Widal reaction is present for a relatively short time in low dilutions after convalescence, and for a longer period and in much higher dilutions after artificial immunization. Nevertheless the immunized individual, both convalescent and artificial, shows great resistance to infection long after the disappearance of the agglutinins, especially the convalescents. This clearly indicates that there is a cellular immunity in addition to the circulating or humoral immunity. *The great excess of the circulating immune bodies in the artificially immunized is of great practical importance in the serotherapy of typhoid fever.*

The previous attempts at specific therapy in typhoid fever, using immune human serum, as mentioned above and reported by von Jaksch,[28] Walger,[29] Petrovitch,[30] and Garbat,[31] failed to appreciate the quantitative differences in the antibody content of convalescent and artificial immune serum. In most of the cases only convalescent serum was used. When one remembers that many convalescent sera show a very low agglutination titer, and occasionally none at all, it is not surprising that these earlier results were not regarded with any great enthusiasm. In the few instances in which artificial immune serum was used very little regard was paid to the length of time after immunization, so that the serum was not obtained at the peak of the antibody content. Furthermore, very small doses of serum were used. This was, of course, a necessity in dealing with convalescents. However, the passive immunity conferred must have been comparatively small.

The present method is attempted in the light of modern theories and experiences in immunity as especially related to typhoid fever. To summarize these very briefly: The immunity produced through infection by the Bacillus typhosus (or the para A and B) shows a very high cellular immunity but a relatively small content of circulating antibodies, the latter rapidly disappearing during convalescence. The immunity produced by prophylactic inoculations shows a very high content of circulating antibodies, disappearing rather slowly, and a relatively low cellular immunity. The index of circulating antibodies is the agglutination titer, no other satisfactory one being available, although it must be realized that the agglutinins represent only one of a number of protective substances.

If the foregoing hypotheses be true, and experience and experiment point in that direction, then the use of blood from recently artificially immunized individuals would seem to be the proper procedure, especially in the very toxic cases. On theoretic grounds the use of whole blood in large quantities offers many advantages. The larger quantities (500 to 700 cc) furnish a great amount of protective substances. The inclusion of the cellular elements of the blood furnishes additional coagulating properties, much needed leukocytes and the red blood cells combat the anemia and emaciation and stimulate the bone-marrow, thus aiding red and white blood cell formation. The use of the large quantity of blood also obeys the well-established rule of serotherapy that an excess of serum should always be employed.

The following two cases are then presented in the way of a preliminary report in support of these theories:

Case I.—E. W. T., male, aged thirty-six years; occupation, clerk.

History. The family history was negative. He had measles and mumps as a child. In 1906 he had a continued fever lasting three weeks, which was said to be typhoid fever, but without laboratory confirmation. He is a great user of tobacco, both smoking and chewing. For the past eight years he had been a constant user of alcohol, consuming about one pint of whisky daily and occasionally a larger amount. He is married and has three healthy children.

The patient was first seen on June 4, 1921, by Dr. E. W. Birch. For two weeks he had been complaining of a moderate malaise and headache, and there had been a nose-bleed one week previously. A specimen of blood taken on June 5 and reported on June 6 showed a positive Widal with the Bacillus typhosus. The patient resided at Fort Meyer Heights, Va., a suburb of Washington, but there had been no other cases of typhoid fever in the immediate vicinity. The well-water on this place showed no fecal contamination and no other members of the family were affected. It was later learned that the patient was very fond of raw oysters and had eaten them frequently during the previous month. On June 7 he was removed to the Sibley Hospital.

June 7 to June 19. The temperature on admission was 104.4°. During this period of twelve days there was practically a continuous temperature, with a minimum of 102.6° and a maximum of 104.6° by the axilla. He was constantly irrational and semicomatose.

June 20 to June 25. During this period of six days the diurnal temperature variations were greater, with a minimum of 99° and a maximum of 103.6°. The delirium and semicoma continued. On June 25, the twenty-second day of the illness, there was a profuse intestinal hemorrhage, accompanied by rapid pulse (160 per minute), pallor, rapid sighing respirations, sweating and collapse. There were no symptoms of perforation. Dr. Thomas A. Claytor saw the patient in consultation and advised blood transfusion, although he gave a very poor prognosis. The writer then saw the patient for the first time for the purpose of transfusion. 600 cc of blood was given by the citrate method, with a very rapid and marked improvement. The blood-pressure before transfusion was 100 mm. and afterward was 108 mm. systolic. The temperature fell to 98° after the hemorrhage, but by the next day was 103.6°.

June 26 to July 4. During this period of eight days following the transfusion the condition of the patient was fairly good. The temperature varied between 100° and 104.2,° with a continuation of the delirium.

July 3 a small quantity of food was given by mouth, the first since the hemorrhage. This was followed by a profuse intestinal hemorrhage. A transfusion of 700 cc was again given (thirtieth day of illness). The symptoms of collapse present after the first hemorrhage were again in evidence, and were as rapidly and effectually ameliorated by the transfusion.

July 5 to July 7. The temperature continued high after the second transfusion, and for this period of three days varied between 100.8° and 104.° However the patient's general condition was not very satisfactory. The delirium was more marked, alternating with periods of complete coma. The emaciation was extreme, and there was a very rapid and shallow pulse. In view of the poor condition of the patient and the catastrophe following the ingestion of food after the first transfusion the writer suggested that another transfusion be given in place of food. It was realized that 600 or 700 cc of blood represented more food than this patient could take in by mouth for quite a few days, that the normal blood might contain some natural protective substances, and, fortunately, there were plenty of donors available. Therefore on July 7 (thirty-third day of disease) a transfusion of 700 cc was given. There was no reaction and the only result of this treatment was some improvement in the patient's general condition. The temperature curve showed no essential changes.

July 8 to July 15. The temperature for this period of seven days following the third transfusion of normal blood varied between 99.6° and 104°. There was no abatement of the very toxic symptoms as enumerated above. Both nurses on the case had offered to be donors, and since both had been artificially immunized when beginning duty on this case it was deemed advisable to try the effect of transfusion with recently immunized blood. Only one of the bloods was found to be in the proper iso-hem-agglutinin group. The Wassermann was negative and the serum was found to have a very high agglutination titer (typhoid, $\frac{1}{12000}$; paratyphoid A, $\frac{1}{7000}$; paratyphoid B, $\frac{1}{5000}$). She had received three doses of the Army Medical School triple vaccine, at one week intervals, and had received the last dose on June 23, 1921, so that this represented the twenty-first day after the last injection.

July 25. A fourth transfusion of 500 cc was given, but this time with recently artificially immunized blood. This was the fortieth day of the disease and the temperature was 103° just before the transfusion. There was no reaction.

July 16 to July 30. On the day following the fourth transfusion the maximum temperature was 100° and by the following day it was 99.2°. During this period of fifteen days the temperature was practically normal, varying between 97.6° and 99.6°. The symptoms of extreme toxemia improved very rapidly. Whereas the temperature was practically normal within thirty-six hours of this transfusion the delirium had practically disappeared in forty-eight hours. The pulse and respirations also showed a proportionate improvement. From this time up to July 30 the condition was one of steady improvement. Food was again allowed in the middle of this period.

July 31 to August 13. On July 31, the fifty-eighth day of the disease, there was a recrudescence of the fever. For the next fourteen days it varied between 99.8° and 101.4,° but there was no return of the delirium, coma, rapid pulse or other toxic symptoms, and the patient continued to take his food without mishap.

August 14 to August 28. This period of fourteen days marked one of steady improvement. The temperature remained normal with the exception of an occasional rise to 99.° He was discharged from the hospital on the eighty-sixth day of the disease.

After a rest of about one month at home he has returned to his work. Upon questioning it is interesting to learn that he remembers nothing of his stay in the hospital until the middle of the first period of normal temperature, about four days after the fourth transfusion. He does not recall anything about the transfusions.

Laboratory Data. The Widal reaction done on June 6 and June 18 was strongly positive with the Bacillus typhosus. The leukocyte counts were as follows: June 6, 2900; June 17, 2200; June 23, 1900; June 28, 3600; July 1, 2700; July 6, 4700. It is interesting to note the rise of leukocytes following transfusion. The erythrocyte counts and hemoglobin estimations made before and after the first two transfusions are not included in this report, as there was some question as to their accuracy. Urine examinations were made at various periods of the case, and there were no pathologic changes with the exception of a faint trace of albumin and a few casts. Both of these disappeared during convalescence.

A summary of this case presents a few outstanding features: the value of transfusion in typhoid hemorrhage is clearly demonstrated in spite of the misgivings expressed in practically every standard text-book. The timeworn axiom that blood-pressure is raised and bleeding increased is a fallacious one, as the systolic pressure is usually only raised from 8 to 10 mm., certainly not enough to increase hemorrhage. The use of blood as a supportive measure and as food in such a case, where there is great inanition and where food is contraindicated, would seem to be of value. But the most striking feature is a comparison of the results of the four transfusions. Three transfusions of normal blood alleviated the symptoms of hemorrhage in two instances and acted in a supportive manner in a third, but the temperature and toxemia were in no way affected. The fourth transfusion of recently artificially immunized blood produced a prompt fall in temperature and a rapid disappearance of the symptoms of toxemia.

CASE II.—A. L. G., female, single, aged twenty-six years, occupation, school teacher.

History. With the exception of mumps, measles, and chickenpox in childhood the patient has never been ill. She has always been very robust and athletic. The family history is uninteresting. The last two weeks of August, 1921, were spent on a farm. On September 6, 1921, she complained of a dull headache and of general muscular pains. Home remedies were tried for several days, but as the symptoms did not disappear and there was an increasing stupor the writer was consulted.

September 9, 1921. The patient was a young woman, quite robust, and appearing very stuporous. A general physical examination was negative with the exception of a markedly coated tongue, tympanites and sluggish reflexes. The temperature was 103.8,° respirations 18 per minute, and the pulse 62 per minute, and slightly dicrotic.

September 10 to September 18. During this period of nine days the temperature varied between 101.2° and 104.6°. There was a gradually increasing stupor, but the patient could be aroused by persistent stimulation. The regimen consisted of sponge baths for hyperpyrexia and a high caloric diet. The blood culture, taken on September 14, was positive for the Bacillus typhosus.

September 19 to September 30. This period was marked by an almost continuous fever, varying between 103° and 104.8°. The stupor had now become complete and there was a delirium, sometimes of the low muttering type and sometimes very agitated. There had been no evidence of hemorrhage or perforation, but the emaciation was extreme. When the diagnosis of typhoid fever had been made all the members of the family had been given typhoid vaccine as a prophylactic. There were two brothers, one of whom was in the same iso-hem-agglutinin group as the patient. With the possibility of using his blood the intervals between his doses of vaccine were shortened to five instead of seven days. He had therefore received his last injection on September 20, 1921. The vaccine used was the triple vaccine of the U. S. Army Medical School. The agglutination titer of his blood serum was $\frac{1}{6000}$ for the Bacillus typhosus, $\frac{1}{3500}$ for Bacillus paratyphosus A and $\frac{1}{3000}$ for Bacillus paratyphosus B. In view of the increasing toxemia and emaciation 650 cc of the recently artificially immunized blood of the brother was given. The temperature just before the transfusion was 104° (September 30, the twenty-fifth day of the disease).

October 1. The patient's general condition is greatly improved. She is much more quiet, takes nourishment better and the maximum temperature was 102.2.°

October 2. The temperature on the second day following the transfusion was practically normal: maximum 99.2,° minimum 97.8°. There is a continuation of the general improvement and much less evidence of toxemia.

October 3. The temperature remained normal and the delirium had entirely disappeared. The patient would now answer questions by nodding the head. Aside from a tremendous asthenia all evidence of the profound toxemia had disappeared on the third day following the transfusion.

October 4 to October 29. This period was one of a slow convalescence. For the first week the temperature would occasionally reach 99.6.° The patient gradually gained weight and strength. When questioned she said that she did not recall the transfusion in any way, and, in fact, she had no recollection of anything from the fourth day after she went to bed until four days after the transfusion.

Laboratory Data. Blood culture on September 14 was positive for Bacillus typhosus. September 10: Erythrocytes 4,645,000, leukocytes 5600, hemoglobin 82 per cent (Dare). The following additional leukocyte counts were made: September 15, 4400; September 19, 2950; September 28, 2100; October 3, 4900. (Note rise of leukocytes after transfusion.) Widal reaction on September 20 and 29 were positive with the Bacillus typhosus. The Bacillus typhosus was found in the urine and the feces. Urine examinations were made at various times. There were no pathologic changes with the exception of a trace of albumin and a few leukocytes and casts, all of which disappeared during convalescence.

One aspect of the typhoid question that naturally presents itself is the question of the necessity for further developments in treatment when our present-day methods of prevention are so well advanced. A study of the available statistics shows that we have beguiled ourselves with a false sense of security. The most recent complete report is contained in the *Twentieth Annual Report of the Bureau of the Census, Mortality Statistics,* for 1919: "The number of deaths from typhoid fever in 1919 is 7860, corresponding to a death-rate of 9.2 per 100,000 population, which is much lower than the rate for 1918 (12.6), and is the record low rate in the period of twenty years from 1900 to 1919 inclusive. It is based on transcripts of death certificates received from the registration area for deaths, which in 1919 had an estimated population of 85,400,437, or 81.2 per cent of the total estimated population of the United States and the territory of Hawaii." It is safe to assume that the total deaths from typhoid fever in this year is about 10,000. The only available data for 1920 is contained in the ninth annual survey of the large cities (100,000 or more).[32] A study of this report shows a very slight general decrease in the death-rate, but even cities with very low averages show an occasional outbreak. The situation in 1921 does not seem to be so favorable. I shall quote from the *Statistical Bulletin,* Metropolitan Life Insurance Company, October, 1921:

"What is the significance of the remarkable increase in the number of deaths from typhoid fever during the months of August and September of this year? The first six months of the year closed without any indication of a check in the rate of decline for this cause of death. The figures for Metropolitan Industrial policyholders for the period January to June showed that there had been a decline of 14 per cent in the typhoid fever death-rate among white persons and 15 per cent among colored persons as compared with the rate of the first six months of last year. But the number of deaths during the third quarter of 1921 has been so large that at the present writing the typhoid fever death-rate for this year to date equals that of last year and is still rising. Unless there is a change in the present situation the year 1921 will close with a higher death-rate for typhoid fever than did 1920.

"From various parts of the country come reports showing that we are right now experiencing numerous local epidemics of typhoid fever. There has been unusual prevalence of the disease in the states of New Jersey, Illinois Pennsylvania, Ohio, New York, North Carolina, Maryland, Georgia, Indiana, Alabama, Kentucky, and Kansas.

"The facts for the last few months indicate that there has been a slackening in the control of this disease. This does not necessarily mean that we shall go back to the periods of high typhoid fever death-rates. With our present-day knowledge of the causes and means of control of typhoid fever we shall probably never again suffer from the high rates of ten years ago. Nevertheless, the check in the decline of the death-rate is a source of great disappointment and suggests further inquiry as to what is at the bottom of the change. Is it necessary in certain states and cities for the health departments to tighten up their control of the sources of distribution of their milk supplies? Has there been any let-down in the sanitation and supervision of water supplies? Are the precautions against carriers as rigidly carried out as they have been in the past? Is the good effect of war-time inoculation wearing off? Is the distribution of antityphoid literature as general or as effective as heretofore? Are markets and other places where food is handled inspected with as much care as formerly?

"These are some of the questions which health officers and sanitarians must ask in view of the recent increase in the typhoid fever death-rate. We have with good reason begun to look upon typhoid fever as a vanishing disease. It is obvious that there is still much work to be done unless we are willing to continue in the unsatisfactory condition of either a stationary or a rising death-rate from typhoid fever."

The method and length of time required to produce a satisfactory artificial immunity is a matter of prime mportance and possibly one of the real objections to this method treatment. Time does not permit a lengthy discussion of this subject here, but a few fundamental facts will be stated. Since the pioneer work of Wright,[32] Pfeiffer and Kolle,[33] and Russell[34] there has been a constant discussion as to the relative value of vaccination with killed cultures, live cultures and sensitized organisms, and also as to the number and size of the dose and the time interval. It has been used on a large scale in the recent war on large bodies of men under control, and the results have been most excellent in all of them, although the methods differed. The British and American armies used killed cultures in a triple vaccine, containing a single strain each of the Bacillus typhosus, paratyphosus A and paratyphosus B, thus constituting a monovalent vaccine. The British used two doses and the Americans three doses at weekly intervals. The French army used a similar vaccine, except that at the direction of Vincent it was made polyvalent, that is, it contained ten strains of the Bacillus typhosus and single strains of the other two organisms. Vincent recommended the use of four doses at weekly intervals, but due to the exigencies of war reduced it to two. The efficacy of the killed culture vaccine as produced at the U. S. Army Medical School and used with remarkable success in millions of individuals during the past few years cannot be questioned. Similar ones are prepared by various boards of health and also commercially. They usually contain 1000 million Bacillus typhosus, 750 million Bacillus paratyphosus A and 750 million paratyphosus B per cc. The dosage is usually 0.5 cc, followed at weekly intervals by 1 cc, three doses in all. By the end of the first week after the last injection the agglutination titer frequently has reached $\frac{1}{1000}$ or $\frac{1}{2000}$, and in ten days it is frequently $\frac{1}{5000}$ or better. However, the time required to obtain a satisfactory antibody content in the blood is, at the minimum, about three weeks. To be of service in the suggested method of treatment this period of immunization must be shortened.

Gay[35] has been able to obtain very satisfactory immunity by giving the doses on alternate days instead of alternate weeks, and believes it could be accomplished by a single dose containing the same number of organisms as the three. It is possible, however, that such a dose might be overwhelming. The crux of the situation may be well defined by quoting Vincent and Muratet.[36]

"What is the quantity of vaccine needed to confer immunity and what is the duration of this immunity? As a matter of fact the immunity and its duration are in direct relation not to the number of the injections, nor even, properly speaking, to the quantity of vaccine injected, but to the number of typhoid bacilli injected."

Vincent further believes that the minimum protecting dose of antigen is between 1300 and 2000 million bacilli. Therefore it is proposed to use, for the purpose of producing a rapid artificial immunity, the vaccine of the U. S. Army Medical School, or a similar one, in three doses of 0.5 cc, 1 cc and 1 cc on alternate days.

Comment. Two cases of typhoid fever of the hypertoxic type are presented. Both were treated with recently artificially immunized blood, and the result in each case has been unusually gratifying. It is not presumed to draw any definite conclusions from two cases. However, a few possibilities suggest themselves.

1. This is not intended as a general treatment for typhoid fever. The mild and moderately severe cases will respond to careful nursing and a high caloric diet.
2. The rationale of this treatment is founded on experimental and clinical facts as they pertain to typhoid immunization.
3. Parenthetically, transfusion for hemorrhage in typhoid fever is justifiable and is the treatment of choice.
4. In this age the opportunity will come to no one man to apply this form of treatment to a large series of cases. It is to be hoped, therefore, that it will be used in the isolated cases and the cases recorded. In this way only will its ultimate usefulness be established.
5. Perhaps it is too much to hope that this may mark the beginning of another epoch in the conquest of this disease and that the annual toll of ten thousand lives in the United States may be reduced to that many hundred.

REFERENCES.

1. Recherches anatomiques pathologiques et thérapeutiques sur la maladie connue sous les noms de fièvre typhoide, J. B. Baillière, 1841.
2. Calorimetric Observations on the Metabolism of Typhoid Patients with and without Food, Arch. Int. Med., 1915, **16**, 887.
3. Die Hydrotherapie des Typhus, Stettin, 1861.
4. Ueber spezifische Behandlung des Abdominal typhus, Deutsch. med. Wchnschr., 1893, **19**, 985.
5. Therapeutic Use of Vaccine in Typhoid Fever, Am. Jour. Med. Sc., 1912, **144**, 350.
6. The Value of Typhoid Vaccine in the Treatment of Typhoid Fever, Am. Jour. Med. Sc., 1915, **149**, 406.
7. Erfahrungen über Praxis und Theorie der Vakzintherapie, Wien. klin. Wchnschr., 1916, **29**, 33.
8. Abortivbehandlung von typhosen Krankheiten, Mitt. d. med. Gesellsch. z. Tokio, 1914, **33**, 21.
9. Zur Frage der Vakzintherapie des Typhus abdominalis, Deutsch. med. Wchnschr., 1914, **49**, 1556.
10. Traitement de la fièvre typhoide par l'or colloidal, Presse méd., Paris, 1916, **14**, 105.
11. Traitement de la fièvre typhoide par l'or colloidal en injections intraveineuses, Bull. Acad. Méd., Paris, 1914, **72**, 421.
12. Toxine typhoide soluble et serum antitoxique de la fièvre typhoide, Prog. méd., 1898, **7**, 245.
13. De l'immunisation active contre la peste, le cholera et l'infection typhique, Ann. Inst. Pasteur, Paris., 1902, **16**, 918.
14. Ueber die Gewinnung und Wirkung von Typhusheilserum, Deutsch. Arch. f. klin. Med., 1910, **98**, 395.
15. Ueber Typhus-Heilserum, Ztschr. f. exper. Path., 1910, **8**, 1.
16. Serotherapie antityphoidique, Bull. de l'Acad. de méd., Paris, 1916, **76**, 114.

17. La Serotherapie de la Febre Typhoide par le serum du Professor Rodet, Presse méd., Paris, 1918, **15**, 473.

18. Traitement de la fièvre typhoide par le serum de Rodet, Bull. l'Acad. de méd., Paris, 1915, **73**, 321.

19. A Bacteriologic and Clinical Study of a Curative Serum for Typhoid Fever, Jour. Am. Med. Assn., Chicago, 1905, **44**, 1504.

20. Ueber de Behandlung des Typhus abdominalis mit Blutserum von Typhusrekonvalenszenten, Verhand. d. Kong. f. inn. Med., Wiesbaden, 1895.

21. Beitrag zur Behandlung des Typhus abdominalis mit Menschlichen Rekonvalescentenblutserum, Centralbl. f. inner. Med., 1898, p. 941.

22. Traitement de la fièvre typhoide par hemoserotherapie dans l'armée serbe, Presse méd., Paris, July 29, 1915.

23. Ein neues Prinzip der Serumtherapie bei Infectionskrankeiten mit besonderer Berücksichtigung des Typhus abdominalis, Deutsch. med. Wchnschr., 1915, **41**, 755.

24. Zur Behandlung des Typhus mit Eigenserum, Therap. d. Gegenw., Berlin, 1915, **57**, 176.

25. Further Observations on the Treatment of Scarlet Fever with Immune Human Serum, Jour. Am. Med. Assn., Chicago, 1919, **73**, 478.

26. The Value of Convalescent Blood and Serum in the Treatment of Influenza Pneumonia, Jour. Am. Med. Assn., Chicago, 1919, **78**, 478.

27. The Treatment of Influenza Pneumonia with Plasma of Convalescent Patients, Jour. Am. Med. Assn., Chicago, 1919, **52**, 34.

28. Loc. cit. 29. Loc. cit. 30. Loc. cit.

31. Convalescent Typhoid Serum in Treatment of Typhoid Fever, Jour. Immunol., Baltimore, 1916, **1**, 387.

32. Typhoid in the Large Cities of the United States in 1920, Ninth Annual Report, Jour. Am. Med. Assn., Chicago, 1921, **76**, 860.

33. Remarks on Vaccination against Typhoid Fever, British Med. Jour., January 30, 1897, p. 256.

34. Experimentelle Untersuchungen zur Frage des Schutzimpfung des Menschen gegen Typhus abdominalis, Deutsch. med. Wchnschr., 1896, **22**, 735.

35. Progress in Antityphoid Vaccination during 1912, Jour. Am. Med. Assn., Chicago, 1913, **61**, 665.

36. Typhoid Fever, p. 165.

37. Typhoid Fevers and Paratyphoid Fevers, 1917; translated by J. D. Rolleston, p. 266.

CONGENITAL ABSENCE OF THE SPLEEN.

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(From the Babies' Hospital.)

OF all the anomalies relating to the viscera, congenital absence of the spleen is one of the rarest. It occurs as a single abnormality, but more frequently is associated with one or more congenital malformations. In all the reported cases it was an accidental discovery at autopsy. Some of the cases occurred in infants while others were in adults who at no time had discoverable symptoms referable to the absence of an important viscus.

CASE REPORT. Andre P., aged three months, of French parentage, was first seen by one of us on November 15, 1921, and on that